ably rarely justified. Acute bacterial pyogenic meningitis is an emergency and the inclusion of chloramphenicol, along with other antibiotics, in the early stages of the illness is justifiable. It is well recognized that the first 24-48 hours are crucial in the treatment of this condition. Furthermore, the rapidity of absorption of chloramphenicol and its ability to diffuse rapidly into the cerebrospinal fluid are very distinct advantages.

Development of newer antibiotics to cope with penicillin-resistant staphylococci has lessened the need for the use of chloramphenicol although there will be times in these infections when circumstances demand the use of this drug because of difficulties related to toxicity or hypersensitivity which forbid the use of other drugs in a particular case.

Physicians with personal experience of fatalities following the use of chloramphenicol will not employ it unless forced to do so. Certainly the days of its common use for hospital staphylococcal infections are past.

CASE REPORT

Infectious Mononucleosis and Jaundice

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INFECTIOUS mononucleosis is associated with a variety of syndromes; the adjective "protean" occurs with depressing frequency in descriptions of the disease. While hepatocellular involvement and damage are very common, frank jaundice is relatively infrequent; Schiff[1] stated that it is present in 5-10% of cases and that it is mild and generally of short duration, while Britton[2] observed that it is increasing in frequency. The purpose of this communication is to report two cases of mononucleosis occurring in a local outbreak which showed severe jaundice from different complications of the underlying disease.

In the first quarter of 1963 there was a moderate outbreak of infectious mononucleosis in Saskatoon. Most of the patients did not present the commonly described clinical syndromes of the classical disease but rather had vague malaise and fever and were found on investigation to have a high proportion of atypical mononuclear cells in the peripheral blood and a positive heterophil antibody test. In several cases malaise and asthenia were prolonged, while in others atypical monocytes and an absolute lymphocytosis persisted for several weeks. Most of these patients were not hospitalized.

CASE 1.—A.I., aged 27 years, was normally robust and employed as a city firefighter. He first attended his physician's office on January 31, 1963, complaining of malaise, weakness and fatigue. These symptoms had begun a month before, and two weeks after their onset he had also noticed dark stools, orange-coloured urine, night sweats and scleral jaundice. He stated that a man with whom he worked had recently been ill with jaundice.

Examination revealed no specific abnormalities apart from the jaundice; in particular, the liver and spleen were not enlarged. A blood count showed slight neutropenia, lymphocytosis and monocytosis, and on later review of the blood film it was felt that many of the monocytes were atypical and characteristic of "glandular fever cells". The results of blood counts throughout the course of the illness are summarized in Table I. His serum bilirubin was 4.0 mg./100 ml., and his serum proteins were 6.3 g./100 ml. with an albumin level of 4.0 g. % and globulin of 2.3 g. %. On February 11 he had a leukocytosis with an absolute lymphocytosis and monocytosis. The serum bilirubin had declined to 1.1 mg./100 ml. and the cephalin-cholesterol flocculation read + in 48 hours. In the blood film many polychromatic macrocytes and basophilic stippled cells were found. The earlier blood film showed the same changes, and the possibility was considered that the jaundice might be due to hemolysis rather than to hepatocellular damage. On February 13 he was admitted to hospital for further investigation.

On admission he stated that his symptoms of weakness and fatigue had begun to regress three days before and that his appetite had improved. Clinical examination showed no abnormality apart from slight scleral jaundice, but radiographs revealed an enlarged spleen. A blood count showed persistence of his lymphocytosis and monocytosis with the presence of atypical monocytes. His serum bilirubin was 1.2 mg./100 ml.; the serum protein level was 6.3 g./100 ml., with albumin 4.2 g. % and globulin 2.1 g. %. The alkaline phosphatase activity was 4.0 Bodansky units. Urinalysis revealed no abnormality and the urine urobilinogen concentration was 0.57 mg./ml. His blood group was O, rhesus-positive (D). A direct Coombs test was negative. Red cell fragility was normal. The Paul-Bunnell test was positive to a dilution of 1/3584 without absorption, negative after absorption with beef erythrocytes, and 1/896 after absorption with guinea-pig kidney.

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TABLE I.—RESULTS OF BLOOD COUNTS IN CASE 1 (A.I.)

	January 31	*February 11*	*February 14*	*February 18*	*February 21*	*February 27*	*April 22*
Hb. (g./100 ml.)	13.4	13.0	12.4	13.6	15.1	16.2	17.7
Erythrocytes/c.mm.			4.07M	4.34M			
Leukocytes/c.mm.	4800	11,750	7000	7500	5300	5450	5250
Neutrophilic leukocytes	11%	17%	18%	26%	25%	29%	43%
Band cells	7%	3%	3%	2%	5%	1%	4%
Metamyelocytes			2%				
Eosinophils	2%	1%		2%		4%	3%
Lymphocytes	62%	69%	62%	53%	45%	56%	43%
Monocytes	17%	10%	3%	5%	4%	4%	3%
Atypical monocytes			12%	12%	11%	6%	4%
Reticulocytes			10.2%	12.5%		5.8%	1.6%
Platelets/c.mm.			150,090				

During his stay in hospital his reticulocyte count varied from 10 to 12.5%. Agglutinins and hemolysins were absent from his serum. The cephalin-cholesterol flocculation test rose from + to ++ on February 16 and to +++ on February 20. Sternal marrow examination showed erythroid hyperplasia, and 2.8% of the nucleated cells in the marrow were atypical mononuclear cells; there was no evidence of a granulomatous reaction.

He was discharged from hospital on February 21, showing continued clinical improvement without specific therapy. By February 27 his reticulocytes had declined to 5% and his atypical mononuclear cells to 6%. On April 22 he was working again and feeling well. His serum bilirubin was minimally elevated at 1.5 mg./100 ml.; the Paul-Bunnell titre had declined to 1/28, and 4% atypical mononuclear cells were present in the peripheral blood. His cephalin-cholesterol flocculation test was negative.

CASE 2.—R.R., aged 34, was employed as a member of the ground staff at the local airport. He called his physician on February 19, 1963, complaining of jaundice, which had been present for several days, and of marked weakness and anorexia. There was no history of exposure to toxins, nor had any of his friends or colleagues suffered from similar symptoms. Examination confirmed the presence of marked jaundice, but the liver and spleen were not felt. He stated that six or seven years previously he had had an attack of jaundice for which he had been off work for about two weeks. Unfortunately no record of this illness can be traced in the files of the physician who attended him at that time. He gave no history of symptoms in the intervening period, and there was no history of illness resembling cholecystitis.

Because of the similarity to Case 1 he was investigated; the hematological and biochemical findings are summarized in Table II. His serum bilirubin, heterophil antibody titre and percentage of atypical mononuclear cells declined steadily but his cephalin-cholesterol flocculation test remained persistently positive. He recovered gradually without specific therapy and returned to work on March 28, feeling fairly well but complaining of being easily fatigued.

DISCUSSION

The association of acute hemolytic anemia with infectious mononucleosis is rare. Thurm and Bassen[3] collected 13 cases from the literature and added two more from their own records. All but one of these showed a diagnostic elevation of the heterophil antibody titre, but the degree of jaundice and the severity of the hemolytic process were very variable. In five of the cases a direct Coombs test was performed and in three it was positive; an additional patient showed the presence of autohemolysins, active at room temperature. Two patients required splenectomy because of continuation of the hemolytic process, but in one of these there was a coincident Mediterranean anemia of long standing; this patient was also the only one of the series to show significant splenic enlargement. The authors felt that in those cases with a

TABLE II.—HEMATOLOGICAL AND CHEMICAL FINDINGS, CASE 2 (R.R.)

	February 19	*February 22*	*March 4*	*March 14*	*March 21*	*April 9*
Hb. (g./100 ml.)	15.0	15.1	14.9	15.1	14.4	16.2
Leukocytes/c.mm.	5850	6950	5850	7500		7950
Neutrophils	15%	56%	63%	59%		66%
Band cells	3%	5%	1%	3%		3%
Eosinophils	3%	2%	2%	3%		1%
Basophils	1%					
Lymphocytes	32%	19%	19%	22%		18%
Monocytes	10%	4%	10%	8%		12%
Atypical monocytes		14%	4%	5%		
Reticulocytes	0.8%		2%	3.2%	3.1%	2.1%
Bilirubin	13.2 mg.%		4.5 mg.%	2.6 mg.%	1.8 mg.%	1.4 mg.%
direct	8.4 mg.%					0.8 mg.%
indirect	4.8 mg.%					0.6 mg.%
Serum protein	6.4 g.%					
albumin	3.1 g.%					
globulin	3.3 g.%					
Inorganic phosphorus	3.2 mg.%		3.3 mg.%		3.4 mg.%	
Alkaline phosphatase (Bodansky units)	9.6		10.3		7.4	8.0
Paul-Bunnell	1/224	1/56	1/7	1/7	1/7	
Cephalin-cholesterol flocculation		++++	+++		++++	+++

demonstrable antibody an autoimmune process best explained the syndrome, but in those in which the direct Coombs test was negative the hemolysis was probably due to hypersplenism. The marrow was examined in almost all the cases of this series and only erythroid hyperplasia was found, a situation comparable to that in our own Case 1. The reported presence of granulomatous lesions in the marrow[3] was not confirmed in our patients. It appears that Case 1 developed an acute hemolytic process fairly early in the course of his infectious mononucleosis, without demonstrable autoantibodies, and that the hemolysis combined with a more slowly developing hepatocellular damage was sufficient to cause clinical jaundice. The process gradually resolved during about six weeks and the marrow was capable of sufficient hyperplasia to maintain the hemoglobin at a practically normal level.

Case 2 demonstrates the commoner occurrence of jaundice due to hepatocellular damage in mononucleosis. The history of a previous attack of jaundice is suggestive of infective hepatitis and tends to exclude that disease as the cause of his reported illness. Schiff stated that the heterophil antibody does not show a significant rise during infectious hepatitis, though atypical lymphocytes may be present in patients with that disease. The heterophil antibody titre was initially elevated in Case 2 and showed a rapid decline; unfortunately, absorption studies were not done on this initial specimen. We felt that the atypical mononuclear cells were characteristic "glandular fever cells", and we have not seen this type of cell in such numbers in patients with infectious hepatitis. In Case 1 the cephalin-cholesterol flocculation reaction increased in strength slowly, attaining a +++ level and declining quickly, and the hepatocellular damage appeared at the most to be a minor factor in the development of jaundice. In Case 2 this test was strongly positive in the first specimen taken and remained strongly positive for a longer time. The elevation of the alkaline phosphatase, while not great, may indicate an obstructive component of the jaundice, as suggested by Schiff. In Case 1 the reticulocyte count declined from a high level as the hemolytic process abated, while in Case 2 as the jaundice cleared there was a slight but definite rise in the reticulocyte count, at a constant hemoglobin level, that may have indicated some decreased life span of erythrocytes. It seems that in both of our cases there was hepatocellular damage and probably hemolysis, of different relative importance and differing speed of development. We have confirmed the findings of slight reticulocytosis and a positive cephalin-cholesterol flocculation test in other cases of mononucleosis in which there was neither jaundice nor other evidence of hemolysis. Rosalki, Jones and Verney,[4] using enzyme studies, found liver involvement to be a usual feature of the disease.

SUMMARY

Two patients who developed jaundice during the course of infectious mononucleosis are described. In one this was due to acute hemolysis and in the other to hepatocellular damage. Both recovered without specific therapy.

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PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

THE PALLIDA UNMOLESTED WORKS

The abolition of paresis lies in the prevention of syphilis, and writers are sadly at variance as to whether antisyphilitic treatment will prevent paresis. Fournier believed it possible. According to him only five per cent. of syphilitics received adequate treatment, while on the other hand, Kriss, Schuster and Junius and Arndt are far from being convinced as to this efficacy of mercurial treatment. The early recognition, in the so-called preparetic stage, probably the incipient period of the degenerative process, is of great importance, since this is the one time favourable for successful therapy. Availing ourselves of the modern methods, we should be governed by Fournier's dictum: "Strike hard, quick and often".

In the presence of paresis and tabes, there is some excuse for therapeutic nihilism. The former is more intractable than the latter to treatment, and both are much less amenable than the other forms of nervous syphilis. Generally speaking, the longer syphilis has existed the more resistent it is to treatment and paresis is one of its late manifestations. Jelliffe aptly says: "It is a question of the inaccessible spirochete." Its habitat in paresis is at a distance from blood vessels and lymph channels; the latter being obstructed interferes with flow of lymph as well as the transmission of therapeutic agents. Thus, the pallida unmolested works out its lethal purpose.

Remissions are nature's attempt at a cure. They develop spontaneously, natural episodes as it were in the course of the disease. The quiet and regular hours of a hospital regime are conducive to their occurrence. Various therapeutic measures, it would seem, are capable of artificially inducing them; viz., first, the prolonged injection of small doses of tuberculin, from 0.01 to 0.1 mg.; second, the injection of bacterial toxins. Kraepelin suggests that since septic organisms hinder the propagation of the spirochetes, it may be possible to use them as allies in the fight against paresis, Third, the use of nucleic acid and metallic ferments. Fischer, every three to five days, injects his paretics with 0.5 gramme of the sodium salt of nucleinic acid in 10 per cent solution. Thus it is believed that by the use of these agents we produce leucocytosis and stimulate the natural defense of the organism against the spirochetal onset. There is not the slightest doubt that treatment can influence, even if it does not arrest, the paretic process, as is shown by a decrease in lymphocytosis and a diminution in the intensity of the Wassermann reaction.—C. E. Riggs: *Canad. Med. Ass. J.*, 4: 20, 1914.